The obvious typographical error on page 1 of the specification noted by the Examiner is corrected by amendment herein. Additional obvious typographical errors are also corrected. No new matter is added.

SUBSTITUTE DECLARATION

A substitute DECLARATION has been prepared and was submitted on October 25, 2000, under separate cover.

BASIS IN PARENT APPLICATION FOR CLAIMS IN THIS APPLICATION AND DEFINITIONS OF EFFECTOR AND REGULATORY CELLS

It is respectfully submitted that pending claims do find basis in the parent application. The specification must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, *i.e.*, whatever is now claimed. Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ.2d 1111, 1117 (Fed. Cir. 1991). The test for new matter is whether the subject matter of a claim is supported by or conforms to the disclosure of an application as filed. The test for sufficiency of support in a patent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." Ralston Purina Co. v. Far-Mar-Co., Inc., 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting In re Kaslow, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)) (see also, MPEP 2163.02). Furthermore, the **subject matter of the claim need not be described literally (i.e., using the same terms or inhaec verba)** in order for the disclosure to satisfy the description requirement.

The specification as originally filed conveys with reasonable clarity disclosure that supports all of the pending claims and the claims of this application as originally filed.

In the parent application, U.S. provisional application Serial No. 60/044,693 (converted to a provisional from application Serial No. 08/506,608) claims recite:

15. (Amended) A method for generating autologous effector immune cells for use in adoptive immunotherapy, the method comprising:

withdrawing leukocyte containing material from a mammal; and
treating the cells to alter their cytokine production profile,
proliferating the cells to a sufficient number for infusion into the mammal adequate for use in the adoptive immunotherapy.

16. The method of claim 15, wherein the leukocyte containing material is purified prior to infusion into the mammal.

19. The method of claim 16, wherein the leukocyte containing material is treated to differentiate into Th1-like cells or Th2-like cells.

26. The method of claim 15, wherein the leukocyte containing material is proliferated to an excess of 1×10^{10} cells.

The parent application is directed to methods for the production of high concentrations and amounts of homogeneous compositions of immune cells, including Th1, Th2, and also LAK, CTL and TIL cells. In the parent application, the term "effector" cell was used to encompass all types of regulatory cells. Dependent claims separated out the Th1 and Th2 cells from the generic type. Claim 1 generically encompassed all types of T cells.

In the instant application, the nomenclature, **not** the intended scope of the claims, was modified so that the generic language refers to what was called effector cells in the parent application as "immune cells" Compare claim 1 as originally in the instant case with claim 1 of the parent case. The language "effector" is changed to immune cell. Further, two classes of cells were defined: regulatory immune cells, which are clearly defined (as discussed below) to include Th1 and Th2 cells, which can be identified by their distinct cytokine profiles and

which act on other cells; and effector immune cells, which are defined as the LAK, CTL, MAK and TIL type cells.

The parent specification states at page 7, line 16. that effector cells include Th1, Th2-like cells. The specification describes Th1 and Th2 cells at page 8, lines 27, page 9, line 3, and page 9, lines 20-24; and states at page 9, lines 25-28:

> Accordingly, it is desirable to have the ability to produce large quantities of autologous Th1 T-cells in disease states where a Th2 cytokine profile predominates (infectious disease) and Th2 T-cells in a TH1-dominant disease (chronic inflammation and autoimmune disease).

Methods for activation of immune cells under conditions to produce Th1 or Th2 cells are described at page 11, lines 11-19.

In the parent specification, production of clinically relevant numbers of cells Th1 cells (and also Th2 cells) is described at page 7, lines 6-25. At page 8, lines 25-, page 9, line 3, the parent specification states that CD4+ cells can be subdivided into TH1 cells and Th2 cells. At page 9, line 25, - page 10, line the parent application states that it is desirable to produce large quantities of Th1 T-cells in disease states where a Th2 cytokine profile predominates, such as in infectious diseases, and to produce large quantities of Th1 cells in diseases in which Th1 cells predominate, such as chronic inflammation and autoimmune disease. The parent application describes large quantities as an "excess of 10^{10} cells (see page 6, line 26, page 7, lines 13-15). At page 10, lines 5=7, the parent application states that:

> The present invention includes a process that enables the production of large quantities of immune cells, such as Th1 and Th2 cells, for use in ACI of human disease.

The process for preparing these cells is described on page 10, line 14, - page 14, line 20). It is exemplified in Example 1, which shows that non-specific $CD4^+$ and $CD8^+$ cells can be expanded to "clinically relevant numbers" (page 30, lines 9-10).

Greater than 10^{10} cells $CD4^+$ and $CD8^+$ were shown to be produced. Example 2 (see page 34 of the parent application) shows preparation of clinically relevant numbers of virally purged $CD4^+$ Th1 cells.

The scope of the claims and subject matter of claims as originally filed and as filed in the instant cased are the same. The definitions were slightly modified in the instant case; but it is clear from the context that broad claims to the general method of inducing activation and proliferation using mitogenic antibodies in the absence of IL-2 (see claims 1-14), and claims in which the cells are caused to differentiate into Th1 or Th2 (or Th1-like or Th2-like) populations of cells prior to proliferation (claims 15-27) cover the same methods.

The parent application states, starting at page 6, line 23, that:

> use of ACI protocols will require technology that enables: the generation of homogeneous populations of immune effector cells [*i.e.*, cells that include TILs, LAKs, CTLs, Th1, Th2 cells]; the consistent growth of effector cells to clinically relevant dosages (*i.e.*, greater than 10^{10} cells) without the use of IL-2; . . . and the ability to reinfuse the cells without the need for systemic infusion of IL-2. Furthermore additional *in vitro* differentiation strategies are need to broaden the types of cells available for ACI protocols.
>
> The present invention addresses each of these requirements, disclosing a method to differentiate Th1 or TH2 cells *in vitro* and grow these cells to clinically relevant numbers without the use of IL-2.

The specification states (page 1, lines 12-16) that ACI is a procedure in which immune cells are harvested, treated *in vitro* and then reinfused. The specification continues by stating the ACI is an attempt to bring the immune system back into regulatory balance by reinfusing large numbers of the cells that were in short supply.

At page 6, line 23, -page 7,line 5, (see, also page 7, lines 13-15), U.S. application Serial No. 08/506,668 states that the use of ACI requires

technology that permits generation of homogenous populations of effector immune cells, the consistent growth of the cells to greater than 10^{10} cells without the use of IL-2 . . . This application [08/506,668] addresses each of these rquirements and provides a method for differentiating "Th1 or Th2 cells *in vitro*" to "clinically relevant numbers without the use of IL-2." At page 10, lines 5-7, the parent application states (08/506,668) that:

> The present invention includes a process that enables the production of large quantities of immune cells, such as Th1 and Th2 cells, for use in ACI of human disease.

In particular, Example 2 describes expansion of HIV- $CD4^+$ cells in the absence of IL-2. Example 2 describes the isolation of $CD4^+$ cells from an HIV patient, activation of the cells with immobilized and CD3 mAB in the presence of IFN-γ, selection for HIV- cells, and then expansion as in Example to produce more than 10^{10} cells. Example 3 shows selection and expansion of CTL cells, in the absence of IL-2, to amounts grater than 10^{10}; and Example 4 shows activation and expansion of HIV- $CD4^+$ cells in the absence of IL-2 to produce greater and 10^{10} Th2 $CD4^+$ cells.

The scope of the claims and subject matter of the claims as originally filed and as filed in the instant cased are the same. The definitions were slightly modified in the instant case; but it is clear from the context that broad claims to the general method of inducing activation and proliferation using mitogenic antibodies in the absence of exogenous IL-2 (see claims 1-14), and claims in which the cells are caused to differentiate into Th1 or Th2 (or Th1-like or Th2-like) populations of cells prior to proliferation (claims 15-27) cover the same methods.

The parent application states, starting at page 6, line 23, that:

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> clinically relevant dosages (*i.e.*, greater than 10^{10} cells) without the use of IL-2; . . . and the ability to reinfuse the cells without the need for systemic infusion of IL-2. Furthermore additional *in vitro* differentiation strategies are need to broaden the types of cells available for ACI protocols.

The present invention addresses each of these requirements, disclosing a method to differentiate Th1 or TH2 cells *in vitro* and grow these cells to clinically relevant numbers without the use of IL-2.

The parent application also makes it abundantly clear that the prior art all disadvantageously (see page 6, line 5, - page 7, line 5)

> include the use of IL-2 as a growth stimulant, requiring Il-2 also to be infused concomitant with the cells . . .. With the exception of the A-LAK protocol, no prior art method attempts to purify the effector cells to generate homogeneous cell populations.. . .
>
> Clinical testing of ACI protocols in cancer has [been] greatly curtailed . . . because the potential efficacy of LAK and TIL therapies has been overshadowed by the substantial toxicity of the treatments. The toxicity is attributed to the administration of systemic IL-2 . . . [that] is necessary in these protocols because lymphocytes differentiated or grown in IL-2 die within 48 hours of IL-2 withdrawal.
>
> Therefore, expanded use of ACI protocols will require technology that enables: the generation of homogeneous populations of effector immune cells; the consistent growth of effector cells to clinically relevant dosages *(i.e., greater than 10^{10}* **cells) without the use of IL-2** . . ..
>
> The present invention addresses each of these requirements disclosing a method to differentiate Th1 or Th2 cells *in vitro* and grow these cells to clinically relevant numbers without the use of IL-2.

This provides clear unequivocal basis for the pending claims in the present application.

The instant application has been rewritten for clarity, not to add new matter to the original claims, and to provide additional examples of applications of the technology. To distinguish between differentiation of cells to produce LAKs, TILs and CTLs, from differentiation to produce Th1, Th2 and Th3 cells and

subcategories thereof, different nomenclature has been adopted. The same cells are encompassed by the claims; their names are different. Changing the names of claimed subject matter does not add new matter if the substance remains substantially the same.

Finally, as discussed below, whether or not basis in the parent application is accorded to some or all of the instant claims is not relevant to the patentability of the instant claims over the cited art and art of record. None of the cited references, singly or in any combination thereof, teaches or suggests methods for preparation of compositions containing predominantly one type of T-cell, nor methods for expansion of such cells in the absence of IL-2.

Prefatory remarks

IMMUNOLOGICAL PARADIGM

Blood contains two main types of regulatory immune cells designated Th1 and Th2 cells (see, *e.g.*, Cherwinski *et al.* (1987) *J Exp Med 166*:1229-44; and Mosmann *et al.* (1986) *J Immunol 136*:2348-2357). Alteration of the balance of these cells leads to devastating disorders such as cancer, autoimmune, infectious and allergic diseases, spontaneous abortion and transplant rejection.

NORMAL IMMUNE SYSTEM

In healthy adults Th1 and Th2 cells are maintained in a carefully regulated balance. When challenged with a virus, the immune system balance changes in favor of Th1 cells. After the virus is eliminated, Th2 cells increase and the immune system returns to balance. Parasitic infections are eliminated by an increase in Th2 cells. An increase in Th1 cells after elimination of the parasite returns the system to normal balance.

CANCER AND INFECTIOUS DISEASE

Patients with advanced cancer or afflicted with infectious diseases (such as AIDS, hepatitis B or C, herpes) have a regulatory immune imbalance in favor of Th2 cells. The excess Th2 cells chronically suppress the body's ability to mount an immune response to eliminate the tumor or virus. Excess Th2 cells are also found in patients with severe allergic diseases such as asthma and in patients with Lupus. Th1 cells are also lost with aging increasing susceptibility to cancer and infectious diseases, cancer, hepatitis C, AIDS and others.

AUTOIMMUNE DISEASE

Patients with autoimmune diseases (such as rheumatoid arthritis, multiple sclerosis, diabetes and inflammatory bowel disease, have a regulatory immune cell imbalance in favor of Th1 cells. The excess Th1 cells mediate a chronic inflammatory condition that destroys the body's own tissues. For example, excess Th1 cells are also responsible for rejecting organ transplants and causing spontaneous abortion

TREATMENTS

The instant application provides immunotherapeutic treatments that act to reduce the magnitude of a Th1/Th2 regulatory cell imbalance have been proven to be therapeutic for many diseases. The technology provided by the instant application is capable of correcting even the most severe Th1/Th2 regulatory cell imbalances, providing hope for millions of patients with devastating diseases for which there currently are no cures or adequate treatments.

This application is directed to methods for generating substantially homogeneous compositions of cells that contain a high concentration of one population of immune cells, and also to methods for treatment of diseases by altering immune balance using such compositions. The claims in this application

are directed to the methods of producing the such substantially homogenous compositions.

As stated at page 12 of the specification:

> Methods of use of regulatory immune cells in autologous cell therapy (ACT) protocols to treat and prevent human disease are provided. The ACT protocols designed to alter the immunoregulatory balance of a patient in order to treat diseases where imbalances in regulatory cells exist. In particular, ACT protocols designed to alter the immunoregulatory balance of a patient in order to treat diseases where imbalances in regulatory cells exist are provided.

There are two major types of regulatory immune cells (formerly under the umbrella of effector cells, but under current terminology **and as defined in the specification)**: Th1 cells, which promote an inflammatory response, and Th2 cells, which act to suppress an inflammatory response. These cells refer to populations of cells in which one cell type predominates; the cell type is defined by its cytokine profile.

The immune system normally maintains these cells in a carefully regulated balance. Imbalances in these regulatory cells are characteristic of many incurable diseases, such as metastatic cancers, autoimmune, allergic and infectious diseases. For example, cancer patients have an excess of Th2 regulatory cells, which suppress the immune system; whereas autoimmune disease patients have an excess of Th1 regulatory cells, which promote an inflammatory response. The methods herein, provide a means to produce high concentrations of one type of immune cell by collecting lymphoid cells, *differentiating* them into substantially one type of immune cell, and then stimulating them to proliferate to high densities. For treatment, the cells are reinfused into the patient to restore immune balance. The type of cell selected depends upon the disease being treated. All of these aspects

are described and disclosed in the parent application U.S. application Serial No. 08/506,668, converted to U.S. provisional application Serial No. 60/044,693.

Traverse of the restriction requirement

The invention lies in the concept of altering immune balance by administering populations of cells that contain predominantly one type of immune cell in a sufficient concentration to alter immune balance in the recipient using a homogenous population of cells; in methods for production of cells for use in the methods, and in the resulting compositions of cells. Methods for preparing compositions for administration are provided as are methods using the compositions; the compositions are also claimed.

There is no burden to examine and search for the broad concepts, the concept of altering immune function by preparing compositions containing high densities of cells of a particular a type.

It also is noted that as originally filed, a restriction requirement issued dividing the case into five groups. In reliance upon that requirement, four divisional application have been filed. In each of these cases, including this case, further election and/or restriction requirements have been imposed resulting in division of the case into what will (if the requirements are maintained) be 25 or more applications. As discussed above, the claims in all cases relate to the same generic concept of producing high concentrations and amounts of homogeneous compositions of cells for infusion in the absence of IL-2 into mammals in order to alter or restore immune system balance. With the exception of original claim 1 and certain claims dependent thereon, the methods involve obtaining immune cells, treating them so that they differentiate into one type of immune cell, and then treating them so that they proliferate into a high number of cells. Dependent claims specify ways of differentiating them, ways of proliferating them, the

products of the differentiation/proliferation methods, and use of the products for treatment. This subject matter does not warrant 25 patent applications and the resulting 25 patents.

The Office is reminded that as between the cancelled claims and any of the presently pending claims in this case and the other co-pending cases based upon the parent application U.S. application Serial No. 08/506,608, obviousness-type double patenting cannot be held. All of these cases and the cases that will be filed have been filed in accord with restriction requirements as set forth by the Office. Additional divisionals in accord with the further restriction requirements will be filed. In no case should a rejection for obviousness-type double patenting be made. See, also MPEP 804.01, which states:

> 35 U.S.C.121, third sentence, provides that wherein the Office requires restriction, the patent of either the parent or any divisional application thereof conforming to the requirement cannot be used as a reference against the other. This apparent nullification of double patenting as ground of rejection or invalidity in such cases imposes a heavy burden on the Office to guard against erroneous requirements for restriction where the claims define essentially the same inventions in different language and which, if acquiesced in, might result in the issuance of several patents for the same invention.

Hence, for example, obviousness-type double patenting cannot be held between claim 48 of this application, and an application in which the subject matter of claim 18 is prosecuted.

Claim 18 is directed to a method of autologous cell therapy, comprising:

collecting material comprising body fluid or tissue containing mononuclear cells from a mammal; and

contacting, in the absence of exogenous interleukin-2, the material with one or more activating proteins specific for cell surface proteins present on cells in the material and in an amount sufficient to induce ex vivo cell expansion, whereby the cells expand to clinically relevant numbers; and

infusing the resulting cells into a mammal.

Claim 48 is directed to a method of autologous cell therapy, comprising:

(a) collecting a tissue or body fluid sample comprising mononuclear cells from a mammal;
(b) activating the cells *ex vivo* to alter their cytokine production profile;
(c) inducing cell proliferation and cell expansion, in the absence of exogenous interleukin-2, by contacting the activated T cells with one or more mitogenic antibodies to produce a clinically relevant number of the T cells; and
(d) reinfusing at least 10^{10} cells.

Claim 48 could have been written as dependent upon claim 18, because it is directed to the same method, except that includes the step of activating the cells to alter their cytokine profile. The Office is now precluded from holding obviousness-type double patenting.

REJECTION OF CLAIMS 48, 51, 124, 126 AND 127 UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 48, 51, 124, 126 and 127 are rejected as being indefinite under 35 U.S.C. § 112, second paragraph. Various bases for this rejection are set forth and each is discussed in turn. This rejection is respectfully traversed.

Relevant Law

When "one skilled in the art would understand all of the language in the claims when read in light of the specification," a claim is not indefinite. Rosemount Inc. v. Beckman Instruments, Inc., 727 F.2d 1540, 1547, 221 USPQ 1, 7 (Fed. Cir. 1984), Caterpillar Tractor Co. v. Berco, S.P.A., 714 F.2d 1110, 1116, 219 USPQ 185, 188 (Fed. Cir. 1983). The claims are definite if they "make clear what subject matter they encompass and thus what the patent precludes others from doing". In re Spiller, 182 USPQ 614 (CCPA 1974). The requirements of § 112, second paragraph are met when one can "examine the claims to see whether the invention's metes and bounds can be adequately determined from the claim languages". In re Goffe, 188 USPQ 131 (CCPA 1975).

Analysis

1. Claims 48 and 124

Claims 48 and 124 are rejected as being indefinite in the recitation of "regulatory immune cells" because the definition in the specification is allegedly unclear.

The specification defines regulatory immune cells as follows (emphasis added):

> As used herein, a regulatory immune cell is any mononuclear cell with a defined cytokine production profile and in which such cytokine profile does not directly mediate an effector function. A regulatory immune cell is a mononuclear cell that has the ability to control or direct an immune response, but does not act as an effector cell in the response. *Regulatory immune cells exert their regulatory function by virtue of the cytokines they produce and can be classified by virtue of their cytokine production profile. For example,* regulatory immune cells that produce IL-2 and IFN-γ, but do not produce IL-4 are termed "Th1" cells. Regulatory immune cells that produce IL-4 and IL-10, but do not produce IFN-γ are termed "Th2" cells. Regulatory immune cells that produce TGF-β, IL-10 and IFN-γ, but do not produce IL-2 or IL-4 are termed "Th3" cells. Cells that produce Th1, Th2 and Th3 cytokine profiles occur in CD4+ and CD8+ cell populations. Cells that produce IL-2, IL-4 and IFN-γ are thought to be precursors of Th1 and Th2 cells and are designated "Th0" cells. Populations of cells that produce a majority of Th1 cytokines are designated "Th1-like"; populations producing a majority of the Th2 cytokines are designated Th2-like"; those producing a majority of Th3 cytokines are designated "Th3-like". Thus, each composition, although containing a heterogeneous population of cells, will have the properties that are substantially similar, with respect to cytokine, to the particular Th subset.
>
> It is understood that this list of T- cells is exemplary only, and any other definable population, array or subtype of T cells that can be expanded by the methods herein to clinically relevant numbers are intended herein.

An effector cell is defined as:

> As used herein, *effector cells are mononuclear cells that have the ability to directly eliminate pathogens or tumor cells. Such cells include, but*

are not limited to, LAK cells, MAK cells and other mononuclear phagocytes, TILs, CTLs and antibody-producing B cells and other such cells.

Hence from the above definition is it clear that Th1, Th2 and Th3 cells, as well as populations of cells designated Th1-like, Th2-like and Th-3-like are regulatory immune cells, and that killer cells, TIL cells, antibody-producing cells and other such cells ere effector cells.

The definitions are not unclear; the skilled artisan could ascertain whether they were infringing a claim directed either regulatory or effector cells. The specification makes it clear that regulatory cells all have distinct cytokine profiles and are defined by their cytokine profiles and their function is by virtue of these cytokine profiles. In contrast, effector cells are mononuclear cells that are not regulatory cells and that like LAK, TILS, MAKs, CTLs and B-cells directly eliminate pathogens by virtue of their direct interaction with pathogens and tumor cells.

Analysis

First, as discussed above, the specification defines regulatory immune cells as follows:

> a regulatory immune cell is any mononuclear cell with a defined cytokine production profile and in which such cytokine profile does not directly mediate an effector function. A regulatory immune cell is a mononuclear cell that has the ability to control or direct an immune response, but does not act as an effector cell in the response. Regulatory immune cells exert their regulatory function *by virtue of the cytokines they produce and can be classified by virtue of their cytokine production profile*. For example, regulatory immune cells that produce IL-2 and IFN-γ, but do not produce IL-4 are termed "Th1" cells. Regulatory immune cells that produce IL-4 and IL-10, but do not produce IFN-γ are termed "Th2" cells. Regulatory immune cells that produce TGF-β, IL-10 and IFN-γ, but do not produce IL-2 or IL-4 are termed "Th3" cells. Cells that produce Th1, Th2 and Th3 cytokine profiles occur in CD4+ and CD8+ cell populations . . ..

Furthermore, these cells are contrasted in the specification to "effector cells, such as LAK, TIL and CTL cells" (see, e.g., page 20), which the specification defines (page 20, lines 23-26) as follows:

> As used herein, effector cells are mononuclear cells that have the ability to directly eliminate pathogens or tumor cells. Such cells include, but are not limited to, LAK cells, MAK cells and other mononuclear phagocytes, TILs, CTLs and antibody-producing B cells and other such cells.

Responses are mediated by virtue of their interaction with a pathogen or tumor cell, not by virtue of their secretion of a cytokine.

The specification continues at page 24, line 27 *et seq.* as follows:

> Regulatory immune cells control the nature of an immune response to pathogens [see, Mosmann, *et al.* (1986) J. Immunol. 136:2348; Cherwinski, *et al.* (1987) J. Exp. Med. 166:1229; and Del Prete, *et al.* (1991) J. Clin. Invest. 88:346]. The different types of responses are attributable to the heterogeneity of $CD4^+$ T cells. $CD4^+$ cells can be sub-divided according to their cytokine expression profiles. These cells are derived from a common precursor, Th0, which can produce Th1, Th2 and Th3 cytokines [see, Firestein, *et al.* (1989) J. Immunol. 143:518]. As noted above, Th1 clones produce IL-2, INF-γ, lymphotoxin and other factors responsible for promoting delayed-type hypersensitivity reactions characteristic of cell-mediated immunity. These cells do not express IL-4 or IL-5. Th1 cells promote cell-mediated inflammatory reactions, support macrophage activation, immunoglobulin (Ig) isotype switching to IgG2a and activate cytotoxic function.
>
> Th2 clones produce cytokines, such as IL-4, Il-5, IL-6, IL-10 and IL-13, and thus direct humoral immune responses, and also promote allergic type responses. Th2 cells do not express IL-2 and IFN-γ. Th2 cells provide help for B-cell activation, for switching to the IgG1 and IgE isotypes and for antibody production [see, e.g., Mosmann *et al.* (1989) Annu. Rev. Immunol. 7:145]. Th3 cell produce IL-4, IL-10 and TGF-β.

> The cytokines produced by Th1 and Th2 cells are mutually inhibitory. Th1 cytokines inhibit the proliferation of Th2 cells and Th2 cytokines inhibit Th1 cytokine synthesis [see, e.g., Fiorentino, *et al.* (1989) Med. 170:2081 (1989). This cross regulation results in a polarized Th1 or Th2 immune response to pathogens that can result in host resistance or susceptibility to infection . . ..

Thus, the nature of regulatory immune cells as opposed to effector cells, which are cells that **directly eliminate pathogens or tumor cells** is clear from the specification.

The Examiner notes that Th1 cells secrete lymphotoxin and urges that this contradicts the definition. It is respectfully submitted that this is in line with the definition provided above. The Th1 cells are mediating activity by virtue of secretion of the lymphotoxin, **not** by direct interaction with cells.

Also as noted previously, Liblau *et al.* does not teach that Th1 or Th2 cells are "effector cells" as alleged by the Examiner. Liblau *et al.* refers to Th1 and Th2 cells as having "**effector function**", this is distinct from the definition of effector and regulatory cells as defined in the instant application. Since these cells participate in the effector phase of an immune response they have effector function, but they do not directly cause the elimination of a target antigen, such as a true effector cell, such as a CTL or TIL cell.

Furthermore, there is no teaching in Liblau *et al.* that pathogenicity in IDDM is caused by Th1 cells directly destroying islet cells such as is known to occur by immune effector cells. Rather, Liblau teaches that **Th1 cells mediate** (i.e. have a regulatory function) the pathogenesis of IDDM **by the types of cytokines they produce**. The ability of Th1 or Th2 cells to mediate disease is characterized by Liblau *et al.* as "effector function" (see page 34, first column, second paragraph, line 8; page 37, legend to Figure 1, line 12), but it does not meant that the cells are effector cells. They are acting in accord with the definition of regulatory cells in the instant application.

There is a distinction in the art between "effector function" as used by Liblau *et al.* in which the cells participate in the effector phase of an immune response, and effector cells, such as, CTLs, B cells or phagocytic monocytes, which directly act to eliminate the target antigen. **Regulatory immune cells participate indirectly in immune responses by elaboration of cytokines.** Although Liblau *et al.* describes that "effector function" is associated with effector and regulatory immune cells, this does not contradict nor confuse the definitions given in the instant application. The definitions in the instant application render it very clear that cells that mediate their function by virtue of their cytokine profile are regulatory cells; and cells the mediate their function by direct interaction with a target are effector cells.

Similarly, the fact that Mossman *et al.* states that TH1 eliminate pathogens by secretion of lymphotoxin; that is not the same as the activity of that of a TIL or CTL that directly eliminate the target cell not by elaboration of a cytokine. Consistent with Liblau *et al.* and Mossman *et al.*, the specification provides separate definitions for regulatory and effector immune cells at page 19 as:

> any mononuclear cell with a defined cytokine production profile and in which such cytokine profile **does not directly mediate an effector function**. A regulatory immune cell is a mononuclear cell that has the ability to control or direct an immune response, but does not act as an effector cell in the response. Regulatory immune cells exert their regulatory function by virtue of the cytokines they produce and can be classified by virtue of their cytokine production profile.

The above definition requires a regulatory immune cell to have a defined cytokine profile, where the cytokines do not directly mediate an effector function. The contemplation of a regulatory cell that indirectly mediates an effector function as defined in the specification is consistent with Liblau *et al.* which demonstrates "effector function" for regulatory T cells. The definition of a regulatory immune

cell in the specification also expressly distinguishes it from an effector immune cell as defined on page 19 as:

> mononuclear cells that have the ability to directly eliminate pathogens or tumor cells. Such cells include, but are not limited to, LAK cells, MAK cells and other mononuclear phagocytes, TILs, CTLs and antibody-producing B cells and other such cells.

Thus, the specification, clearly distinguishes an immune regulatory cell from an immune effector cell. The definition in the specification of a regulatory immune cell encompasses Th1, Th2 and Th3 cells, and this is not inconsistent with the concept of "effector function" as described by Liblau *et al.*

2. **Claims 48 and 124** Claim 48 is allegedly indefinite in the recitation of "alter the *in vivo* regulatory immune balance" and claim 124 is allegedly indefinite in the recitation of "altering the regulatory balance of immune cells." As discussed above, the application is directed to methods of altering the immune cell balance by administering clinically relevant numbers of substantially homogeneous populations of cells. The application describes numerous examples of what is meant in the context of treatment of diseases, including cancer, autoimmune diseases, viral and other infectious disease and others (see discussion, "Prefatory Remarks" above and pages 42-49 and elsewhere in the specification. See also page 11, which states:

> Also provided are methods of treatment of disorders, including infectious diseases and autoimmune diseases. In addition, methods of treatment for immunosuppression permitting organ or tissue transplantation and methods for enhancement of vaccination protocols are provided. The treatment methods use the compositions.

At page 15, for example, the specification states:

> The method above is useful for therapeutic treatment of disorders characterized by imbalances in regulatory immune cells. Specifically, the methods provided herein can be used to develop treatments for chronic inflammation in disorders such as, but not limited to, multiple sclerosis, rheumatoid arthritis, Crohn's Disease, autoimmune thyroid disease and

inflammatory bowel disease; chronic infectious diseases such as infections with human immunodeficiency virus, herpes simplex virus, cytomegalovirus and hepatovirus; allergic and other hypersensitivity disorders such as asthma; and provides a method for specific immunosuppression in organ and tissue transplant procedures and a method to provide immunoprotection in vaccination.

Furthermore, the specification defines what is meant by immune balance:

> As used herein, *immune balance* refers to the normal ratios, and absolute numbers, of various immune cells that are associated with a disease free state. Restoration of immune balance refers to restoration to a condition in which treatment of the disease or disorder is effected whereby the ratios of regulatory immune cell types and numbers thereof are within *normal range or close enough thereto so that symptoms of the treated disease or disorder are ameliorated*. The amount of cells to administer can be determined empirically, or, preferably, by administering aliquots of cells to a patient until the symptoms of the disease or disorder are reduced or eliminated. Generally a first dosage will be at least 10^9-10^{10} cells. In addition, the dosage will vary depending upon treatment sought. As intended herein, about 10^9 is from about 5 x 10^8 up to about 5 x 10^9; similarly about 10^{10} is from about 5 x 10^9 up to about 5 x 10^{10}, and so on for each order of magnitude.

As stated at page 12 of the specification:

> Methods of use of regulatory immune cells in autologous cell therapy (ACT) protocols to treat and prevent human disease are provided. The ACT protocols [are] designed to *alter the immunoregulatory balance of a patient in order to treat diseases where imbalances* in regulatory cells exist. In particular, ACT protocols designed to alter the immunoregulatory balance of a patient in order to treat diseases where imbalances in regulatory cells exist are provided.

Hence the specification teaches what is meant by immune balance (normal ratios and absolute numbers of certain cells), that certain diseases arise out of an imbalance, and that treatment of such imbalance are designed to alter immune balance to treat diseases.

Also provided are methods of treatment of disorders, including infectious diseases and autoimmune diseases. In addition, methods of treatment for immunosuppression permitting organ or tissue transplantation and methods for enhancement of vaccination protocols are provided. The treatment methods use the compositions.

Hence the specification clearly defines what is meant by a treatment involving altering the *in vivo* immune cell balance: immune balance is defined, the purpose of the treatments are described, the numbers of cells to administer are described, and throughout the specification exemplary treatments are provided

THE REJECTIONS OF CLAIMS 48 and 51 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

New matter rejection

Claims 48 and 51 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing new matter. The Examiner urges that there is no disclosure in the specification of the method of claim 48 "which recites mammal." This rejection is respectfully traversed.

Relevant Law

The purpose behind written description requirement is to ensure that the patent applicant had possession of the claimed subject matter at the time of filing of the application In re Wertheim, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). The manner in which the specification meets the requirement is not material; it may be met by either an express or an implicit disclosure.

35 U.S.C. §112 requires a written description of the invention. This requirement is distinct from and not coterminous with the enablement requirement:

> The purpose of the 'written description' requirement is broader than to merely explain how to 'make and use'; the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes

> of the 'written description' inquiry, whatever is now claimed." Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563-64, 19 USPQ2d at 1117 (emphasis in original).

The issue with respect to 35 U.S.C. §112, first paragraph, adequate written description has been stated as:

> [d]oes the specification convey clearly to those skilled in the art, to whom it is addressed, in any way, the information that appellants invented that specific compound [claimed embodiment] Vas-Cath, Inc. v. Mahurkar, at 1115, quoting In re Ruschig, 390 F.2d 1990, at 995-996, 154 USPQ 118 at 123 (CCPA 1967).

A specification must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, *i.e.*, whatever is now claimed. Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ.2d 1111, 1117 (Fed. Cir. 1991). A written description requirement issue generally involves the question of whether the subject matter of a claim is supported by or conforms to the disclosure of an application as filed. The test for sufficiency of support in a patent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." Ralston Purina Co. v. Far-Mar-Co., Inc., 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting In re Kaslow, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)) (see also, MPEP 2163.02).

An objective standard for determining compliance with the written description requirement is "does the description clearly allow persons of skill in the art to recognize that he or she invented what is claimed." In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ.2d 1614, 1618 (Fed. Cir.1989). The Examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in an applicant's disclosure a description of the invention

defined by the claims. In re Wertheim, 541 F.2d 257, 265, 191 USPQ 90, 98 (CCPA 1976); *See also* Ex parte Sorenson, 3 USPQ.2d 1462, 1463 (Bd. Pat.App. & Inter. 1987). By disclosing in a patent application a device that inherently performs a function or has a property, operates according to a theory or has an advantage, a patent application necessarily discloses that function, theory or advantage, even though it says nothing explicit concerning it. The application may later be amended to recite the function, theory or advantage without introducing prohibited new matter. In re Reynolds, 443 F.2d 384, 170 USPQ 94 (CCPA 1971); and In re Smythe, 480 F. 2d 1376, 178 USPQ 279 (CCPA 1973).

The guidelines promulgated by the U.S. PTO embody these rules:

> In rejecting a claim, set forth express findings of fact regarding the above analysis which support the lack of written description conclusion. These findings should:
>
> (1) identify the claim limitation not described; and
>
> (2) provide reasons why a person skilled in the art at the time the application was filed would not have recognized the description of this limitation in view of the disclosure of the application as filed.

Furthermore, as noted above, the subject matter of the claim need not be described literally (*i.e.*, using the same terms or *inhaec verba*) in order for the disclosure to satisfy the description requirement.

In this instance, there is no basis to conclude that a person skilled in the art at the time the application was filed would not have recognized the description of this limitation in view of the disclosure of the application as filed.

Basis for the recitation of "mammal" in claim 48 may be found in claim 48 as originally filed in the parent application U.S. application Serial No. 08/700,565 and also in claims 15 and 16 of U.S. application Serial No. 08/506,668.

Claim 48 in U.S. application Serial No. 08/700,565 recites (emphasis added):

> 48. A method of treating patients with autologous immune cells, comprising:
> collecting a tissue or body fluid sample comprising mononuclear cells *from a mammal*;
> treating the cells ex vivo to produce compositions containing clinically relevant number of regulatory immune cells; and
> *reinfusing* a sufficient number of the cells to alter the in vivo regulatory immune cell balance.

Claim 48, thus, states that the cells are collected from a mammal and then, after treatment, reinfused.

Claims 15 and 16 of U.S. application Serial No. 08/506,668 recite:

> 15. (Amended) A method for generating autologous effector immune cells for use in adoptive immunotherapy, the method comprising:
> withdrawing leukocyte containing material *from a mammal*; and
> treating the cells to alter their cytokine production profile,
> proliferating the cells to a sufficient number for *infusion into the mammal* adequate for use in the adoptive immunotherapy.
>
> 16. The method of claim 15, wherein the leukocyte containing material is purified prior to infusion into the *mammal*.

The original claims contemplated adoptive immunotherapy in which leukocyte-containing material is withdrawn from a mammal and then reinfused into the mammal. Furthermore, claim 48, as originally filed recites mammal in the claim and clearly contemplates autologous immunotherapy. Therefore, there is basis in this application and in the parent applications for the recitation of "mammal" in the claims 48 and 51.

Scope of Enablement rejection

Claims 48 and 51 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art how to make and use what is claimed. The Examiner alleges that the specification is not

enabling for methods in which regulatory immune cells per se are generated; the Examiner urges that regulatory immune cells encompass non-T cells, such as dendritic cells. This rejection is respectfully traversed.

Analysis

First it is noted that as defined in the specification, NK cells, macrophages, etc. are *not* regulatory immune cells; they fall within the definition of effector cells because they are not exerting their effect by virtue of their cytokine profile, but rather directly mediate their effects.

Secondly, the specification is not limited to the use of CD3 or CD2 cells for activation, but rather describes method for expanding immune cells per se without the use of IL-2 by treating the cells with mitogenic proteins, particularly mitogenic antibodies (see, pages 32-33 in the specification). These methods are disclosed for effector and regulatory cells (previously encompassed by the term effector cell in the grandparent application).

Third, there is no requirement in the US Patent laws to specifically exemplify every embodiment within the scope of the claims. The specification describes methods for proliferation and expansion of effector cells, including CTLs, LAKS, TILS, and also proliferation and expansion of regulatory cells, such as Th2 and Th1 cells.

Fourth, as amended the claims recite that the cells are T-cells, thereby rendering this ground for rejection moot.

REJECTION OF CLAIMS 44, 51, 124 and 127 UNDER 35 U.S.C. § 102(e)

Claims 44, 51, 124 and 127 are rejected under 35 U.S.C. §102(e) as being anticipated by Babbitt *et al.* (U.S. Patent No. 5,766,920) because Babbitt *et al.*

discloses methods for producing Th1 cells and allegedly expanding the cells. This rejection is respectfully traversed.

First, it is noted that the claims are clear in their scope and that as discussed above, one of skill in the art and one of ordinary skill in the art could ascertain what cells are considered regulatory T cells and what cells are effector T cells in view of the specification.

Relevant law

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. In re Spada, 15 USPQ2d 1655 (Fed. Cir, 1990), In re Bond, 15 USPQ 1566 (Fed. Cir. 1990), Soundscriber Corp. v. U.S.. 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention". In re Lang, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover it is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co., 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. An inherent property has to flow naturally from what is taught in a reference In re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

The claims

Claim 48 is directed to a method of autologous cell therapy by collecting a tissue or body fluid sample containing mononuclear cells from a mammal; activating the cells *ex vivo* to alter their cytokine production profile to produce

activated T cells; inducing cell proliferation and cell expansion, in the absence of interleukin-2 by contacting the activated T cells with one or more mitogenic antibodies to produce a clinically relevant number of T cells selected from Th1, Th1-like, Th2-like and/or Th2 cells; and reinfusing at least 10^{10} cells. Claim 51 recites that the cells are Th1-like cells. Claim 127 specifies that the cells are Th1 cells. Claim 124 is directed to a method for altering the regulatory balance of immune cells in a human, by administering to the human a composition that contains at least 10^{10} Th1 cells.

Differences between the disclosure of Babbitt *et al.* and the claims

Babbitt *et al.* is directed to a method for producing immunoreactive cells by contacting a first sample of mononuclear cells with OKT3 at or below 37° C to "produce an OKT-3-derived culture supernatant (T3CS)", removing the T3CS from the mononuclear cells; optionally supplementing the T3CS with additional OKT3 to produce a concentration of at least 0.1 ng/ml of OKT3, and then contacting a second sample of mononuclear cells with the T3CS to produce immunoreactive cells. The T3CS is conditioned medium that contains autologous cytokines to promote differentiation of Th1 cells.

Hence Babbitt *et al.* is directed to a method for producing activated cells. Babbitt *et al.* does not teach any method for proliferating the activated cells in the absence of IL-2 nor does it teach inducing proliferation using mitogenic monoclonal antibodies. Teachings regarding expansion of the cells contemplates using IL-2 to effect expansion (see column 18, lines 7 -20) and does not disclose or suggest use of mitogenic antibodies for this purpose. Also, as exemplified in Babbitt *et al.*, expansion only produces 10^{9} cells, not the 10^{10} cells contemplated in the instant application. Thus, Babbitt *et al.* does not teach a method for producing clinically relevant numbers for infusion of at least 10^{10} cells, in which expansion is effected

in the absence of exogenous IL-2. Babbitt *et al.* does not teach or suggest a step of expanding the cells to clinically relevant numbers in the absence of IL-2.

Therefore, since the instant claims explicitly recite that expansion is effected in the absence of IL-2, Babbitt *et al.* does not anticipate any of the claims in this application.

THE REJECTION OF CLAIMS 44, 51, 124, 126 and 127 UNDER 35 U.S.C. § 103(a)

Claims 44, 51, 124, 126 and 127 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Babbitt *et al.* (U.S. Patent No. 5,766,920) because Babbitt *et al.* teaches methods for producing Th1 cells by removing patient mononuclear cells are removed and activating and expanding them in the presence of IFN-γ enriched supernatant and OKT3 (anti-CD3 antibody) to produce Th1 cells and then reinfusing the cells. The Examiner states that Babbitt *et al.* differs from the instant claims in that only 10^9 cells are administered concludes it would have been an obvious design choice to have administered 10-fold more cells. This rejection is respectfully traversed.

Relevant law

In order to set forth a prima facie case of obviousness under 35 U.S.C. §103, the differences between the teachings in the cited reference must be evaluated in terms of the whole invention, the prior art must provide a teaching or suggestion to the person of ordinary skill in the art to have made the changes that would produce the claimed product. See, e.g., Lindemnann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co., 730 F.2d 1452, 1462, 221 USPQ 481, 488 (Fed. Cir. 1984). The mere fact that prior art may be modified to produce the claimed product does not make the modification obvious unless the prior art suggests the desirability of the modification. In re Fritch 23 USPQ 1780 (CAFC 1992); see, also, In re Papesh, 315 F.2d 381, 137 USPQ 43 (CCPA 1963).

The Claims

The claims are discussed above. Claim 126 recites that at least 10^{11} cells are reinfused.

Teachings of the cited reference and differences from the instant claims

Babbitt *et al.*

The disclosure and teachings of Babbitt *et al.* are discussed above. Briefly, Babbitt *et al.* is directed to a method for producing activated cells by preparing a T3CS, and incubating mononuclear cells with the T3CS and OKT3. For expansion of these cells, Babbitt *et al.* states:

> Following the incubation of cells with T3CS, the cells may be removed from the T3CS and contacted with IL-2, preferably in an amount which is sufficient to bind to at least 25% of the IL-2 receptors on the surface of the immunoreactive cells; more preferably, the amount of IL-2 is sufficient to saturate the IL-2 receptors on the surface of the immunoreactive cells. Contacting the immunoreactive cells with IL-2 is preferably done at 4° C, during storage or delivery of the cells prior to administration to the patient.

Babbitt *et al.* also states:

> Utilizing T3CS as a stimulant for mononuclear cells, it is possible to generate T cells expressing high levels of CD25/IL-2 receptors, independent of the inclusion of high levels of exogenous IL-2 in the culture medium. Although low levels of IL-2 are present in both the T3CS and EVA cultures at early timepoints, there is no detectable (&lt 6 pg/ml) autologous IL-2 present in the T3CS when the EVA culture is initiated. Consequently, in contrast to LAK and TIL cells which are both cultured in high levels of IL-2, the immunoreactive cells generated by the inventive process are presumably *less* dependent upon systemic administration of high dose IL-2 for therapeutic efficacy. In addition, the lack of IL-2 in the T3CS allows the production of mmunoreactive cells, i.e., multifunctional, polyclonal T cells containing both $CD8^+$/cytotoxic T cells and a high percentage of $CD4^+$/helper cells, in contrast to PBMC grown in high dose IL-2 which are highly enriched in CD8+/cytotoxic T cells. Thus, the immunoreactive cells of the invention have broader functional capacities than PBMC cultured in IL-2.

Hence Babbitt *et al.* teaches activation of the cells in the absence of Il-2, but does not teach expansion of the cells in the absence thereof nor does Babbitt *et al.* teach or suggest the use of mitogenic antibodies for inducing proliferation. Babbitt *et al.* contemplates using IL-2 to effect expansion (see column 18, lines 7 -20). Thus, Babbitt *et al.* does not teach or suggest a method for producing clinically relevant numbers of cells in which expansion is effected in the absence of exogenous IL-2 and in the presence of a mitogenic antibody. Babbitt *et al.* does not teach or suggest a step of expanding the cells to clinically relevant numbers in the absence of IL-2 and does not teach or suggest reinfusion of at least 10^{10} cells.

There is no suggestion in Babbitt *et al.* for modification of its method which relies on production of a condition supernatant and a single antibody to produce activated cells. There is no suggestion of a method in which the cells are treated with a first signal that induces activation followed by a second signal, treatment with mitogenic antibodies, that induces proliferation in the absence of IL-2.

Furthermore, Babbitt *et al.* teaches that its method results in 10^9 cells, but does not teach or suggest means to produce 10^{10} cells for infusion. Going from 10^9 cells to 10^{10} cells would require infusion of 10-fold more cells and the concomitant increase in infused volume. If the 10^9 cells are contained in a volume of a liter, infusion of 10^{10} cells would require infusion of 10 liters of cells. Such difference is non-trivial such that a routineer could have "administered more or less cells" depending upon the patient and disease. There are teachings or suggestions in Babbitt *et al.* for increasing the numbers of cells infused nor any suggestion of a means to do so.

As noted above, the prior art must provide a teaching or suggestion to the person of ordinary skill in the art to have made the changes that would produce the claimed product. See, e.g., Lindemnann Maschinen-fabrik Gmbh v. American Hoist

and Derrick Co., 730 F.2d 1452, 1462, 221 USPQ 481, 488 (Fed. Cir. 1984). The mere fact that prior art may be modified to produce the claimed product does not make the modification obvious unless the prior art suggests the desirability of the modification. In re Fritch 23 USPQ 1780 (CAFC 1992); see, also, In re Papesh, 315 F.2d 381, 137 USPQ 43 (CCPA 1963). IN this instance, the cited reference provides no teachings or suggestions for modifications of its method to treat the activated cells with a mitogenic antibody in the absence of IL-2 nor is there a suggestion for infusing at least 10^{10} cells.

Therefore, the Examiner has failed to set forth a prima facie case of obviousness.

* * *

In view of the above remarks and the amendments and remarks of record, consideration and allowance of the application are respectfully requested.

Respectfully submitted,
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